Trifluridine-tipiracil with bevacizumab for treating metastatic colorectal cancer [ID6298]

Contains no confidential information

Technology appraisal committee B [15 May 2024]

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Trifluridine-tipiracil with bevacizumab for treating metastatic colorectal cancer

- ✓ **Background**
- ❑ Clinical effectiveness
- ❑ Clinical key issues
- ❑ Modelling and cost effectiveness key issues
- ❑ Summary

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Background on metastatic colorectal cancer

Causes and epidemiology

- Adenocarcinoma of the colon or rectum that has spread – mostly to liver, lung or peritoneum
- Usually develops from benign polyps – these are common in people over 50 years of age
- UK incidence is 77 cases per 100,000 - fourth most common cancer in the UK

Prognosis and impact

- Site of primary tumour influences symptoms, prognosis, treatment response and patient QoL
- 56% of metastatic CRC diagnosed patients die within first year, compared to 2% of patients diagnosed with stage 1 CRC
- Fatigue, drowsiness, memory problems and neuropathy can affect ability to work
- Large burden on caregivers as disease progresses

Abbreviations: CRC, colorectal cancer, QoL, quality of life

Patient perspectives

Colorectal cancer is a life-changing disease and trifluridine-tipiracil with bevacizumab would provide additional hope for patients

Submission from Bowel Cancer UK

Living with the condition

- Life-changing diagnosis affecting every aspect of daily life
- Overall experience described as helpless, tough, hard and extreme
- People undergoing treatment for advanced bowel cancer experience range of side effects – significantly affect QoL (physically and emotionally)

"Mentally it turned my world upside down… it never leaves you and you cannot plan anything more than two months ahead because you bounce from scan to scan."

Unmet need

- Extremely limited treatment options and limited timely access on the NHS
- Financial implications for accessing treatments (i.e. fundraising/borrowing for private healthcare) causes unnecessary stress, worry and anxiety

"NHS treatment varies and is a postcode lottery"

Trifluridine-tipiracil with bevacizumab

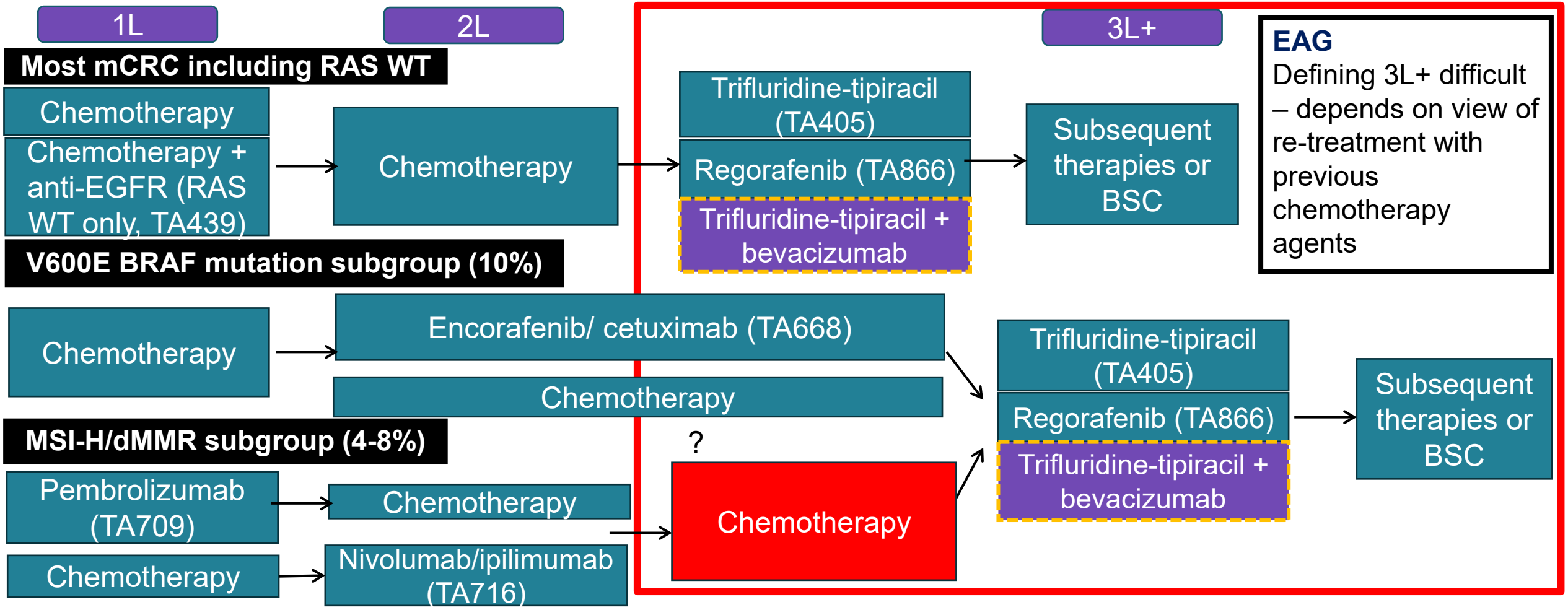
- Access would provide hope due to life-prolonging potential

Abbreviations: QoL, quality of life

Treatment pathway

*Chemotherapy=FOLFOX, FOLFIRI, CAPOX, FOLFOXIRI (or 5-FU, oxaliplatin/irinotecan)

Trifluridine–tipiracil with bevacizumab is being considered for 3L+ in the mCRC pathway



EAG
Defining 3L+ difficult – depends on view of re-treatment with previous chemotherapy agents

EAG clinical expert – people with V600E BRAF mCRC would not have encorafenib/cetuximab at 3L

Does this accurately reflect the current mCRC treatment pathway? Would the intervention be used at any other point in the pathway?

MSI, microsatellite instability; MMR, mismatch repair; 5 FU, 5-fluorouracil; FA- folinic acid; FOLFOX, folinic acid, fluorouracil and oxaliplatin; FOLFIRI, folinic acid, fluorouracil and irinotecan; CAPOX, capecitabine and oxaliplatin; BSC, best supportive care; EGFR, epidermal growth factor receptor

Trifluridine-tipiracil (Lonsurf, Servier Laboratories) with bevacizumab

Marketing authorisation	"Lonsurf is indicated in combination with bevacizumab for the treatment of adult patients with metastatic colorectal cancer (CRC) who have received two prior anti-cancer regimens including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents"
Mechanism of action	• Trifluridine is incorporated into DNA of tumour cells and inhibits tumour proliferation. • Tipiracil hydrochloride prolongs the action of trifluridine. • Bevacizumab binds to VEGF-A to prevent interaction with VEGF receptors, preventing formation of tumour blood vessels.
Administration	• Trifluridine-tipiracil – oral tablets, twice daily (days 1 to 5 and 8 to 12 of each 28-day cycle) • Bevacizumab – intravenous infusion, once every 2 weeks
Price	• Confidential patient access scheme price available for trifluridine-tipiracil • Multiple confidential commercial medicines unit prices available for bevacizumab (biosimilars available)

Abbreviations: VEGF, Vascular endothelial growth factor; EGFR; epidermal growth factor,

Decision problem

	Final scope	Company	EAG comments
Population	Adults with mCRC after 2 systemic treatments	As in scope	Agree
Intervention	Trifluridine-tipiracil with bevacizumab	As in scope	Agree
Comparators	• Trifluridine-tipiracil monotherapy • Regorafenib • BSC • Single agent irinotecan (after FOLFOX) • Raltitrexed (if 5-FU/FA are not suitable) • FOLFIRI (after either FOLFOX or CAPOX) • Encorafenib with cetuximab • Nivolumab with ipilimumab	• Trifluridine-tipiracil monotherapy* • Regorafenib† • BSC† ○ Irinotecan and raltitrexed rarely used in clinical practice ○ FOLFIRI and encorafenib with cetuximab used 2nd line ○ Nivolumab with ipilimumab relevant for high MSI	Agree – EAG clinical expert agrees with company's justification
Outcomes	• OS, PFS, response rate, adverse effects of treatment, HRQoL	As in scope	Agree

- *Direct trial evidence available for comparison with trifluridine-tipiracil monotherapy
- †NMA evidence presented for comparison with regorafenib and BSC

Abbreviations: mCRC, metastatic colorectal cancer; BSC, best supportive care

Key issues

Issue	ICER impact
Comparators	Large
Prior bevacizumab use	Large
Overall survival extrapolation (trifluridine-tipiracil with bevacizumab arm)	Large
Overall survival and progression-free survival extrapolation (regorafenib [comparator] arm)	Very small
Time on treatment (regorafenib arm)	Moderate
Treatment specific utilities	Moderate
Severity modifier	Large
Commercial Medicines Unit (CMU) price range for bevacizumab	Large

Trifluridine-tipiracil with bevacizumab for treating metastatic colorectal cancer

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Key clinical trial – SUNLIGHT trial (NCT04737187)

Clinical trial designs and outcomes

	SUNLIGHT
Design	Open label, randomised, controlled two-arm phase 3 trial
Population	Adults with unresectable, refractory mCRC who had received a maximum of two prior chemotherapy regimens containing fluoropyrimidines, irinotecan, oxaliplatin and anti-VEGF, and/or (in patients with RAS WT tumours) an anti-EGFR antibody therapy
Intervention	Trifluridine-tipiracil with bevacizumab
Comparator	Trifluridine-tipiracil monotherapy
Duration	Intervention arm median follow up: 14.2 months Comparator arm median follow up: 13.6 months
Primary outcome	OS
Key secondary outcomes	PFS, ORR, DCR, TEAEs, QoL
Locations	13 locations - Spain, Russia, Brazil, Hungary, Italy, Poland, France, Ukraine, Denmark, USA, Austria, Germany and Belgium (no UK patients)
Used in model?	Yes

Abbreviations: mCRC, metastatic colorectal cancer; VEGF, vascular endothelial growth factor; WT, wild type ; EGFR, endothelial growth factor receptor; OS, overall survival; PFS, progression free survival; ORR, overall response rate; DCR, disease control rate; TEAE, treatment-related emergent adverse events; QoL, quality of life

See appendix for CORRECT study details

SUNLIGHT: Key clinical trial results overview

Outcome	Results	
	Trifluridine-tipiracil with bevacizumab (n=246)	Trifluridine-tipiracil monotherapy (n=246)
Primary outcome		
Median overall survival, months	10.78 (95% CI: 9.36 to 11.83)	7.46 (95% CI: 6.34 to 8.57)
Overall survival HR	0.61 (95% CI 0.49 to 0.77, p<0.001)	
Secondary outcomes		
Median PFS, months	5.55 (95% CI: 4.50 to 5.88)	2.40 (95% CI: 2.07 to 3.22)
TEAEs		
Trifluridine-tipiracil-related, n (%)	221 (89.8%)	200 (81.3%)
Bevacizumab-related, n (%)	119 (48.4%)	N/A

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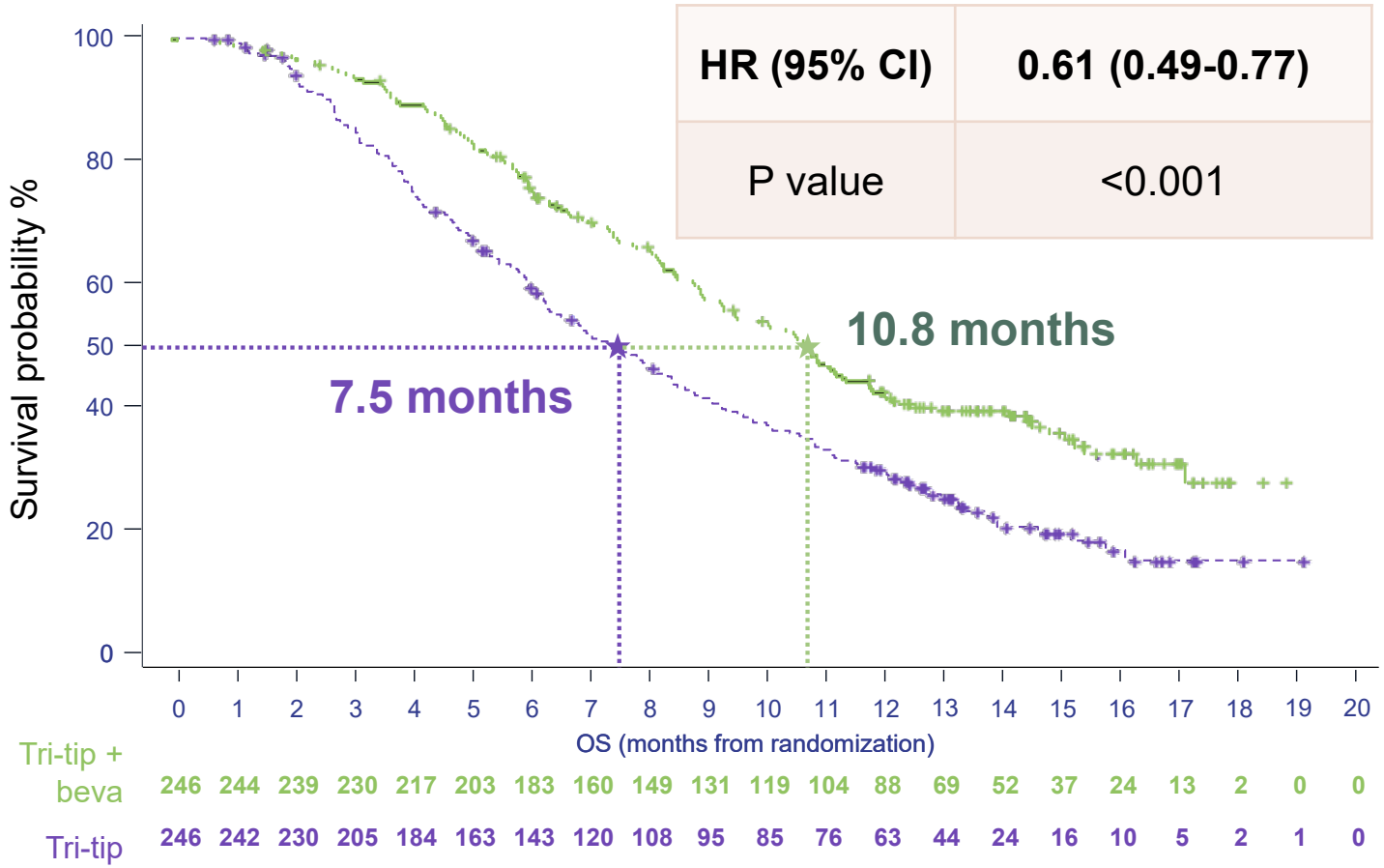
Abbreviations: CI, confidence interval; AE, adverse events; N/A, not applicable; TEAEs, treatment-emergent adverse events; PFS, progression free survival

SUNLIGHT: overall survival

Trifluridine-tipiracil with bevacizumab improves OS vs trifluridine-tipiracil monotherapy

Figure: Kaplan-Meier curve for OS for mCRC (SUNLIGHT)



	Trifluridine-tipiracil with bevacizumab (n=246)	Trifluridine-tipiracil monotherapy (n=246)
Median OS, months (95% CI)	**10.78 (9.36 to 11.83)**	**7.46 (6.34 to 8.57)**
Survival probability		
6 months (95% CI)	77% (72% to 82%)	61% (55% to 67%)
12 months (95% CI)	43% (36% to 49%)	30% (24% to 36%)
18 months (95% CI)	28% (19% to 37%)	15% (9% to 22%)

Are these plausible estimates for overall survival?

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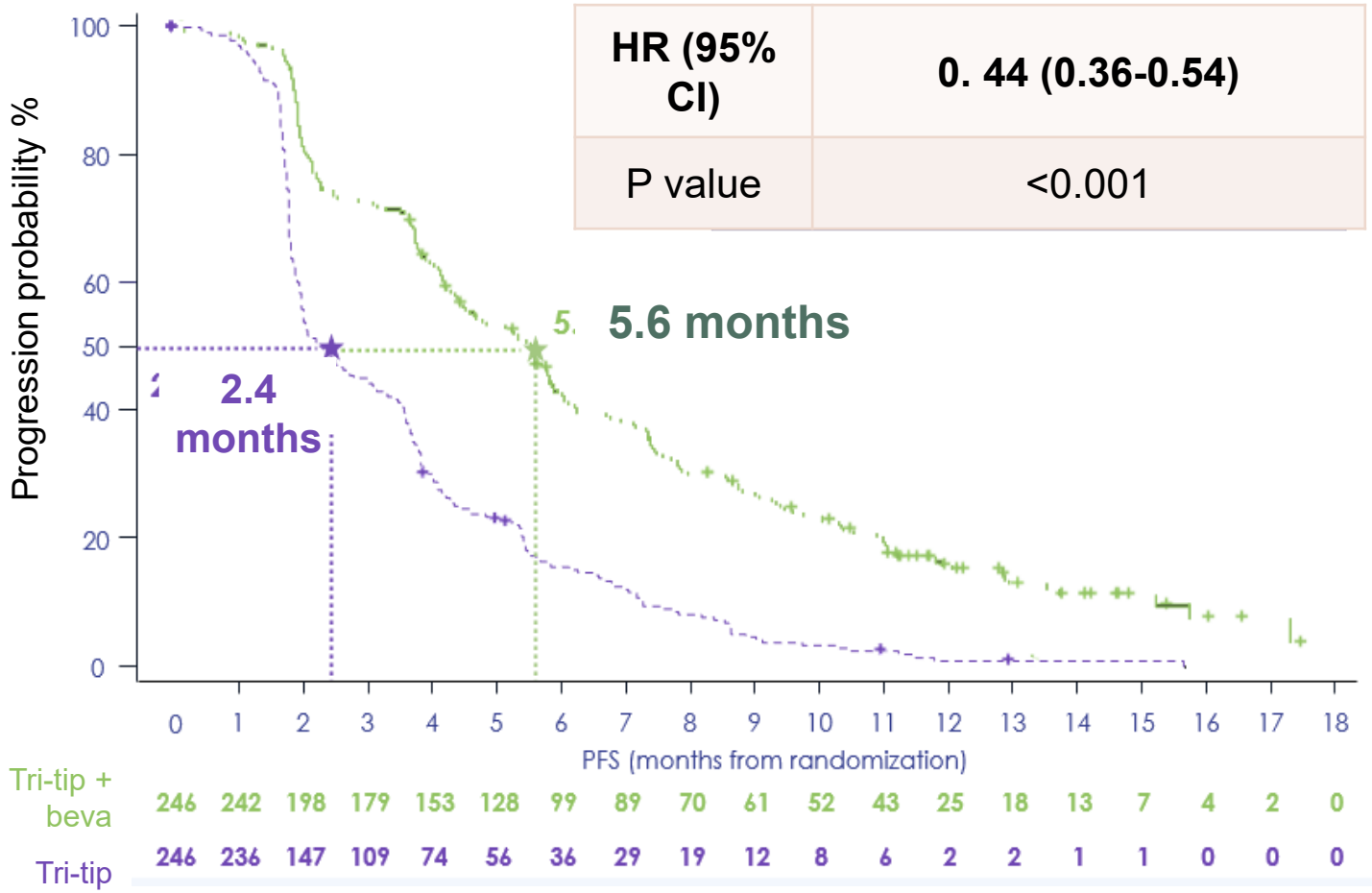
Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival; mCRC, metastatic colorectal cancer

SUNLIGHT: progression-free survival

Trifluridine-tipiracil with bevacizumab improves PFS compared to trifluridine-tipiracil monotherapy

Figure: Kaplan-Meier curve for PFS for mCRC (SUNLIGHT)



	Trifluridine-tipiracil with bevacizumab (n=246)	Trifluridine-tipiracil monotherapy (n=246)
Median PFS, months (95% CI)	**5.55 (4.50 to 5.88)**	**2.40 (2.07 to 3.22)**
Survival probability		
3 months (95% CI)	73% (67% to 78%)	45% (39% to 51%)
6 months (95% CI)	43% (37% to 49%)	16% (11% to 21%)
12 months (95% CI)	28% (22% to 34%)	5% (3% to 9%)
18 months (95% CI)	16% (12% to 21%)	1% (0% to 3%)

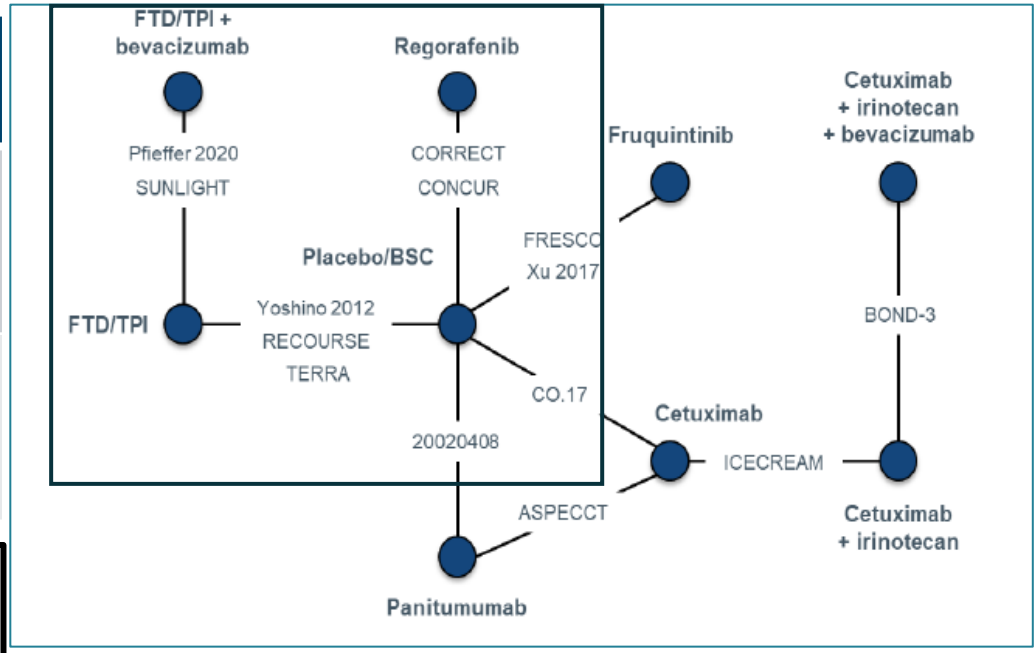
Are these plausible estimates for progression-free survival?

Abbreviations: CI, confidence interval; HR, hazard ratio; PFS, progression free survival; mCRC, metastatic colorectal cancer

Network meta-analysis results

NMA results based on constant HRs – fixed and random effect results similar

Random effects		Trifluridine - tipiracil	Regorafenib	Placebo/ BSC
Median OS (months) (95% CI)	**Trifluridine-tipiracil + bevacizumab**	0.59 (0.43 to 0.79)	0.60 (0.38 to 0.95)	0.41 (0.28 to 0.58)
Median PFS (months) (95% CI)	**Trifluridine-tipiracil + bevacizumab**	0.46 (0.34 to 0.64)	0.49 (0.31 to 0.84)	0.21 (0.14 to 0.31)



Company: Results based on PH assumption - may affect reliability of extrapolations at certain time points

EAG comments:

- Company approach is robust – OS for mCRC <30% at 18 months, so long-term effects of extrapolations based on constant HRs unlikely to be an issue
- EAG clinical expert – differences in number of prior therapies across trials would not significantly impact fitness of participants vs SUNLIGHT trial population.

Abbreviations: OS, overall survival; PFS, progression free survival; HR, hazard ratio; CI, confidence interval

*See appendix for further information on NMA methods

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Key issues: Comparators

Trifluridine-tipiracil, regorafenib and BSC all considered appropriate

Background

- NICE final scope includes 9 comparators – CS comparators are trifluridine-tipiracil, regorafenib and BSC

Company

- Choice of comparators is consistent with TA866
- Company clinical experts – trifluridine-tipiracil, regorafenib and BSC are all current practice in 3L+ mCRC

EAG comments

- Comparators in CS are appropriate and reflective of UK clinical practice
- Exclusion of remaining comparators is justified

Other considerations

- Relevant comparators in TA866 (published Feb 2023) - trifluridine-tipiracil and BSC
- NICE BIA – intervention would be expected to displace trifluridine-tipiracil monotherapy and regorafenib
- CDF clinical lead – trifluridine-tipiracil has better toxicity profile vs regorafenib. It is possible to have both trifluridine-tipiracil and regorafenib, but most will have trifluridine-tipiracil first

Which of trifluridine-tipiracil, regorafenib and BSC are relevant comparators?
Are these treatments interchangeable or is there a difference in the populations receiving each treatment?

Abbreviations: BSC, best supportive care; CS, company submission; mCRC, metastatic colorectal cancer

Key issue: Prior bevacizumab use

SUNLIGHT prior bevacizumab use differs from UK clinical practice

Background

- In SUNLIGHT, most people previously treated with bevacizumab (72%) – not routine UK practice

Company

- Base case reflects ITT population with additional subgroup analysis of people with no prior bevacizumab
- SUNLIGHT ITT results may underestimate effects of trifluridine–tipiracil + bevacizumab in UK population
  - Clinical feedback to company - people with no prior bevacizumab may achieve better response
- Prior bevacizumab use not considered a treatment effect modifier – ITT population generalisable to UK

EAG comments

- Company's approach is appropriate – ITT population appropriate for decision making
- EAG clinical expert – bevacizumab use earlier in treatment pathway may increase over time
- No significant subgroup effects, but point estimate for treatment effect larger with no prior bevacizumab

Previous appraisals – committee conclusions

- TA405 - trifluridine–tipiracil similarly effective in people who have or have not had bevacizumab – results of trials generalisable to NHS patients in England who have not had bevacizumab
- TA866 – pooled results of phase 3 regorafenib studies with prior bevacizumab use likely generalisable to NHS

Do many people have bevacizumab at first or second line – is this expected to change over time?
How might prior bevacizumab use affect clinical effectiveness of the intervention?
Is the ITT population still appropriate for decision making despite prior bevacizumab use?

ITT, intention to treat

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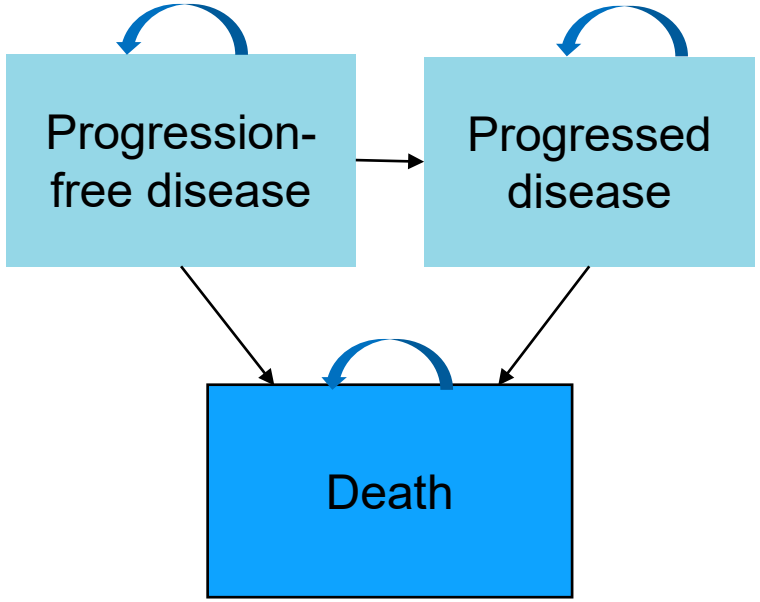
Model overview

Cohort partitioned survival model - EAG says model structure is appropriate

Model structure:



Trifluridine-tipiracil with bevacizumab affects **QALYs** by:

- Increasing time in OS and PFS states → better survival and QoL
- Improved QoL in progression-free disease
- Improved QoL vs comparators (in progression-free and progressed states)

Trifluridine-tipiracil with bevacizumab affects **costs** by:

- Increased acquisition costs (2 treatments instead of 1)
- Additional administration costs for IV bevacizumab
- Increased treatment acquisition and administration costs due to longer time on treatment – mainly since patients spend longer progression-free)

Assumptions with greatest ICER effect:

- Modelling of long-term overall survival for trifluridine-tipiracil + bevacizumab and trifluridine-tipiracil monotherapy
- Source of data for OS, PFS and ToT for regorafenib

- OS, PFS and ToT for trifluridine-tipiracil with bevacizumab and trifluridine-tipiracil monotherapy estimated from SUNLIGHT - regorafenib and BSC health effects obtained from random-effects NMA

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio OS, overall survival; PFS, progression free survival; QoL, quality of life; ToT, time on treatment; NMA, network meta-analysis

How company incorporated evidence into model

Input	Assumption and evidence source
Baseline characteristics	SUNLIGHT study population (48% female, starting age of 62)
Intervention and comparator efficacy	Trifluridine-tipiracil with bevacizumab: SUNLIGHT study, ITT population Trifluridine-tipiracil monotherapy: SUNLIGHT study, ITT population Regorafenib and BSC: Random effects NMA
Time horizon	15 years
Cycle length	1 week (no half cycle correction)
Discount rate	3.5% for costs and QALYs
Utilities	Treatment-dependent HSUVs from SUNLIGHT EQ-5D-5L mapped to EQ-5D-3L
Costs	BNF, NHS NCC, PSSRU and eMIT
Resource use	Routine monitoring costs (outpatient appointments, primary care, CT scans) in line with TA405 and TA886. AE costs based on incidence in SUNLIGHT. One off terminal care cost applied to all patients sourced from literature and updated to 2022 prices using PSSRU inflation indices
Severity modifier	Calculated using SUNLIGHT baseline characteristics
Subsequent treatment	One off cost. Distribution from pooled SUNLIGHT data, equal across treatment arms.
Treatment waning	None

BNF; British National Formulary; NCC, National Cost Collection; PSSRU, Personal Social Services Research Unit; eMIT, electronic market information tool (eMIT); HSUV, health state utility values; ITT, intention to treat; NMA, network meta-analysis; QALY, quality-adjusted life year

Key Issue: Appropriate overall survival extrapolation

EAG and company disagree on most appropriate OS extrapolation

Company

- Fitted a range of parametric survival curves: most provide good statistical and visual fit
- Log-logistic most appropriate to model overall survival, informed by clinical opinion

EAG comments

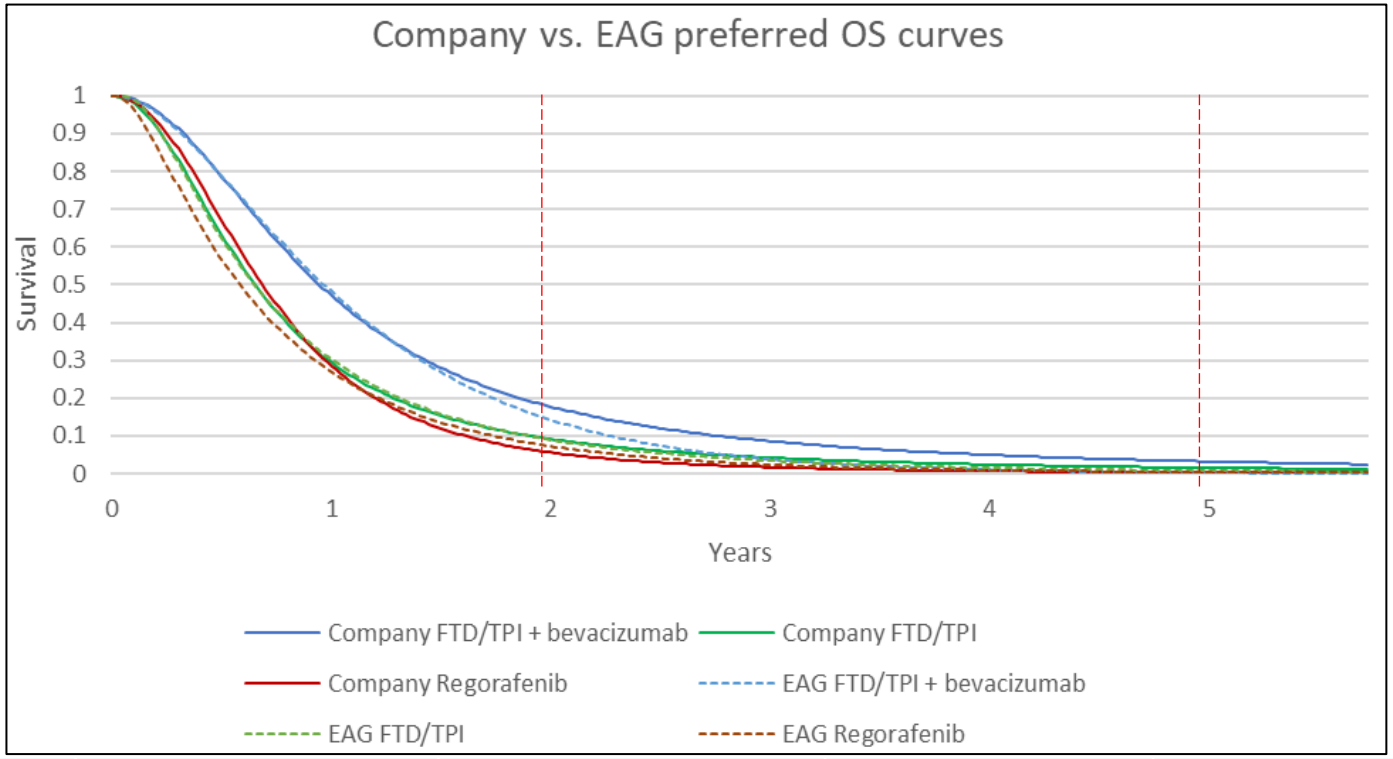
- Most parametric curve fits are plausible, choice should reflect plausibility of long-term projections
- EAG clinical expert – few patients will remain alive at 5 years, regardless of treatment arm; projections over 1% at 5 years lack face validity
- Company clinical expert saw data before giving views
- Magnitude of treatment effect estimated at year 2 by log-logistic fitted to both arms exceeds treatment effect from 1 year KM data (1.95 vs 1.5 respectively)
- Generalised gamma more appropriate – steeper decline in early survival in line with company and EAG clinical expert opinion

How should overall survival be modelled? Company = log-logistic. EAG = generalised gamma.

Abbreviations: KM, Kaplan-Meier; OS, overall survival

Key Issue: Appropriate overall survival extrapolation

EAG and company disagree on most appropriate OS extrapolation



Extrapolations only – KM curves in appendix

How should overall survival be modelled? Company = log-logistic. EAG = generalised gamma.

Year	Log-logistic (Company)	Generalised gamma (EAG)	Clinical expert opinion	Log-logistic (Company)	Generalised gamma (EAG)	Clinical expert opinion
	Trifluridine-tipiracil monotherapy OS			Trifluridine-tipiracil with bevacizumab OS		
2	8.5%	8.2%	2 to 10%	16.6%	12.8%	15 to 20%
5	1.4%	0.7%	"Few if any"	2.9%	0.2%	2.9%*

Abbreviations: FTD/TPI, trifluridine-tipiracil; OS, overall survival

*when provided with model output, stated 2.9% reasonable

Key issue: Modelling regorafenib OS and PFS

Company

- Hazard ratios for trifluridine-tipiracil with bevacizumab vs regorafenib from NMA
- OS and PFS for regorafenib obtained by applying hazard ratio to curves for trifluridine-tipiracil with bevacizumab

EAG comments

- Company and EAG survival curves for trifluridine-tipiracil with bevacizumab are AFT survival curves
- Applying HRs to AFT curves needs proportional hazards assumption to hold - not met
  used CORRECT study (Phase 3 RCT comparing regorafenib vs placebo) to fit independent survival curve for regorafenib
- Differences between SUNLIGHT and CORRECT trials:
  - greater number of prior metastatic drug regimens in CORRECT vs SUNLIGHT
  - all participants in CORRECT had prior bevacizumab
- Limitations for using CORRECT trial – naive comparison with SUNLIGHT trial
- Neither EAG or company's approach ideal, but on balance naïve comparison probably less biased than NMA

How should regorafenib OS and PFS be modelled?

Abbreviations: AFT, accelerated failure time; HR, hazard ratio; OS, overall survival; PFS, progression free survival; NMA, network meta-analysis.

Key issue: Regorafenib time on treatment (ToT)

Company

- Regorafenib ToT data not publicly available - unable to fit ToT curves to observed data or conduct NMA
- Assumed ToT equal to PFS for regorafenib in base case (i.e. stop due to disease progression or unacceptable toxicity only) – in line with SmPC recommendation and approach in TA866
- Company expert – regorafenib may be stopped before progression (i.e. there may be time between discontinuation and progression)

EAG comments

- Clinical expert agrees with company expert that regorafenib treatment may be stopped before progression
- Company's assumption likely overestimates ToT and treatment acquisition costs
- EAG approach assumes a proportion (68%) of those progression-free at any time are on treatment (calculated as mean ToT from CORRECT study divided by mean modelled PFS)
- EAG's approach provides greater consistency with CORRECT ToT study data - regorafenib median ToT:
  - CORRECT: 7.4 weeks
  - EAG approach: 8.8 weeks
  - Company approach: 14.0 weeks

TA866 EAG conclusion

- PFS as proxy for ToT via generated HR only holds up if disease progression and adverse event profiles are similar between regorafenib and trifluridine-tipiracil arms

Is the company or EAG approach to modelling regorafenib time on treatment preferred?

Abbreviations: NMA, network meta-analysis; PFS, progression free survival; SmPC, summary of product characteristics; ToT, time on treatment

Key issue: Use of treatment specific utilities in model

Company = different utilities for tri-tip with bevacizumab, EAG = same for all

Company

- Used EQ-5D data from SUNLIGHT and mixed-effect regression model (controlling for treatment-arm and health state)
- Company's clinical experts prefer higher utility for tri-tip + bevacizumab due to higher response rate

EAG

- Treatment-specific utilities not supported by company's alternative regression modelling – interaction terms between treatment and health state are not statistically significant
- Company's choice of regression model not adjusted for baseline utility – when adjusted the treatment effect is no longer significant
- Preferred base case uses same utility for all treatments (pooled from SUNLIGHT data)

	Company utility	EAG utility	TA866 utility
Trifluridine-tipiracil with bevacizumab			
Progression-free	0.779	0.759	-
Progressed	0.702	0.681	-
Trifluridine-tipiracil monotherapy, regorafenib, BSC			
Progression-free	0.737	0.759	0.72
Progressed	0.659	0.681	0.57

TA866 accepted utilities

Equal pre- and post-progression values for trifluridine–tipiracil and regorafenib (pooled from CORRECT regorafenib study)

Are treatment-specific utility values appropriate?
Which set of utility values should be used?

Key issue: Severity modifier

SUNLIGHT population characteristics: starting age 62, 48% female

	Trifluridine-tipiracil monotherapy	Regorafenib	Placebo/ BSC
Company preferred base case results (deterministic)			
QALYs without disease	12.01	12.01	12.01
QALYs with disease	0.62	0.56	0.42
Absolute shortfall	11.39	11.45	11.59
Proportional shortfall	94.84%	95.34%	96.50%
QALY weight	**x1.2**	**x1.7**	**x1.7**
EAG preferred base case results (deterministic)			
QALYs without disease	12.01	12.01	12.01
QALYs with disease	0.61	0.55	0.43
Absolute shortfall	11.4	11.46	11.58
Proportional shortfall	94.92%	95.42%	96.42%
QALY weight	**x1.2**	**x1.7**	**x1.7**

Criteria for QALY weighting:

QALY weight	Absolute shortfall	Proportional shortfall
1	Less than 12	Less than 0.85
x1.2	12 to 18	0.85 to 0.95
x1.7	At least 18	At least 0.95

- Size of QALY weight varies by comparator
- Company and EAG agree on QALY weighting across all comparators
- TA866 - Regorafenib vs BSC 1.7x, no weighting vs trifluridine-tipiracil due to uncertainty around QALY shortfall estimation (based on indirect treatment comparison)

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Is it appropriate to apply a QALY weighting for severity? What QALY weightings are preferred vs each comparator?

*Further information on QALY severity weighting

Summary of base case assumptions for key issues

Assumption	Company base case	EAG base case
Comparators	Tri-tip monotherapy, regorafenib, BSC	Tri-tip monotherapy, regorafenib, BSC
Prior bevacizumab use	ITT population still appropriate	ITT population still appropriate
Tri-tip + bevacizuma and tri-tip monotherapy OS	Log-logistic curve	Generalised gamma curve
Regorafenib OS and PFS	HR from random-effects NMA	Independently fitted using CORRECT data
ToT for regorafenib	ToT is equal to PFS	Apply proportion of PFS curve on treatment
Utilities	Tri-tip + bevacizumab = 0.779 PF, 0.702 progressed Tri-tip monotherapy, regorafenib, BSC = 0.737 PF, 0.659 progressed	Treatment pooled (0.759 PF, 0.681 progressed)
Severity modifier	x1.2 QALYs for tri-tip monotherapy, x1.7 QALYs for regorafenib and BSC	x1.2 QALYs for tri-tip monotherapy, x1.7 QALYs for regorafenib and BSC


= large impact on ICER (other changes have small to moderate impact on ICER individually)

= Company and EAG agreement

BSC, best supportive care; ITT, intention to treat; HR, hazard ratio; NMA, network meta-analysis; OS, overall survival; PF, progression free; PFS, progression-free survival; ToT, time on treatment

Subsequent treatment distribution

Analysis	Source	Data
Company base case	SUNLIGHT trial	58.3% receive a distribution of subsequent treatments, independent of trial arm
EAG base case	Clinical opinion	58.3% receive subsequent treatment Tri-tip (+/- beva) → regorafenib and regorafenib → tri-tip
EAG scenario	NHSE estimates	As per EAG base case with proportions receiving subsequent treatment based on NHSE data

EAG comments

- Combinations of treatments received in SUNLIGHT do not match UK clinical practice – and retreatment with the same treatment at 4th line would be unlikely (high proportion of retreatment with regorafenib).
- Increased PFS with more effective treatments may increase chances of patients being sufficiently fit to receive another line of treatment – but observed differences in SUNLIGHT are small and the impact of any biases on the ICER is likely to be minimal
- All subsequent treatments have an assumed duration of 2 months, which is likely to be appropriate

NHSE snapshot data of current UK practice

- Attrition is a higher percentage for regorafenib because of higher adverse event burden

	Tri-tip > regorafenib	Regorafenib > Tri-tip
3L	1200	500
4L	500	100

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Is the company or EAG approach to modelling subsequent treatments preferred?

Additional differences in company and EAG base case assumptions

Each additional difference has small impact on ICERs

Assumption	Company base case	EAG base case and justification
Regorafenib RDI	Equal to trifluridine-tipiracil	Uses data from CORRECT study – more accurately reflects treatment specific RDI, consistent with preferred data source for OS, PFS and ToT
Regorafenib monitoring costs	Monthly outpatient (similar to trifluridine-tipiracil)	Additional monitoring costs for regorafenib - associated with additional toxicity, more monitoring needed
Costs for BSC	£1.44	£13.94 per cycle - consistent with TA866 resource use
Calcium folinate post progression treatment	Drug tariff price	eMIT price

Abbreviations: OS, overall survival; PFS, progression-free survival; RDI, relative dose intensity; ToT, time on treatment,

Key issue: CMU price of bevacizumab

Background

- Biosimilars for bevacizumab are available to the NHS at contract prices negotiated through the Commercial Medicines Unit (CMU) – these are lower than the list price but are commercial in confidence
- Different regional CMU prices are available for bevacizumab – 3 scenarios were considered to explore this uncertainty:
  - using the midpoint of the highest and lowest prices across the regions
  - using the single lowest of the regional prices
  - using the single highest of the regional prices.
- The impact of CMU pricing of bevacizumab is confidential and will be reported in Part 2

Other considerations:

- **Equality** - Trifluridine-tipiracil with bevacizumab is not expected to raise any equalities issues
- **Managed access** - The company has not submitted a managed access proposal for trifluridine-tipiracil with bevacizumab

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts

Summary of cost-effectiveness results

When **all** confidential discounts are applied

Company ICERs

- Base case - fully incremental ICERs above the range normally considered an effective use of NHS resources at x1 and x1.2 severity modifier, <£30,000 per QALY gained using 1.7x modifier

EAG ICERs

- Base case - ICERs higher than the range normally considered for cost-effectiveness regardless of the severity modifier applied
- EAG's preferred overall survival modelling for trifluridine-tipiracil + bevacizumab and trifluridine-tipiracil monotherapy has the biggest impact on ICERs followed by pooled utility values
- EAG scenario analyses of company base case increased or did not change ICERs in all scenarios except for calcium folinate eMIT costing and EAG preferred post progression costs
- With lowest CMU price of bevacizumab, ICERs still above standard cost-effectiveness range

Abbreviations: ICER, incremental cost-effectiveness ratio; CMU, Commercial Medicines Unit; QALY, quality-adjusted life year

33

Trifluridine-tipiracil with bevacizumab for treating metastatic colorectal cancer

- ❑ Background
- ❑ Clinical effectiveness
- ❑ Clinical key issues
- ❑ Modelling and cost effectiveness
- ✓ **Summary**

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Summary of key issues for discussion

Key questions raised:

- Which of trifluridine-tipiracil, regorafenib and BSC are relevant comparators?
  - Are these treatments interchangeable or is there a difference in the populations receiving each treatment?
- Do many people have bevacizumab at first or second line – is this expected to change over time?
- How might prior bevacizumab use affect clinical effectiveness of the intervention?
  - Is the ITT population still appropriate for decision making despite prior bevacizumab use?
- How should overall survival be modelled? Company = log-logistic. EAG = generalised gamma.
- How should regorafenib OS and PFS be modelled?
- Is the company or EAG approach to modelling regorafenib time on treatment preferred?
- Are treatment-specific utility values appropriate? Which set of utility values should be used?
- Is it appropriate to apply a QALY weighting for severity?
  - What QALY weightings are preferred vs each comparator?
- Is the company or EAG approach to modelling subsequent treatments preferred?

Abbreviations: BSC, best supportive care mCRC; OS, overall survival; PFS, progression free survival; ITT, intention to treat; QALY, quality-adjusted life year

35

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Thank you.

Trifluridine-tipiracil with bevacizumab for treating metastatic colorectal cancer [ID6298]

Supplementary appendix

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Key clinical trial – CORRECT trial (NCT01103323)

Clinical trial designs and outcomes

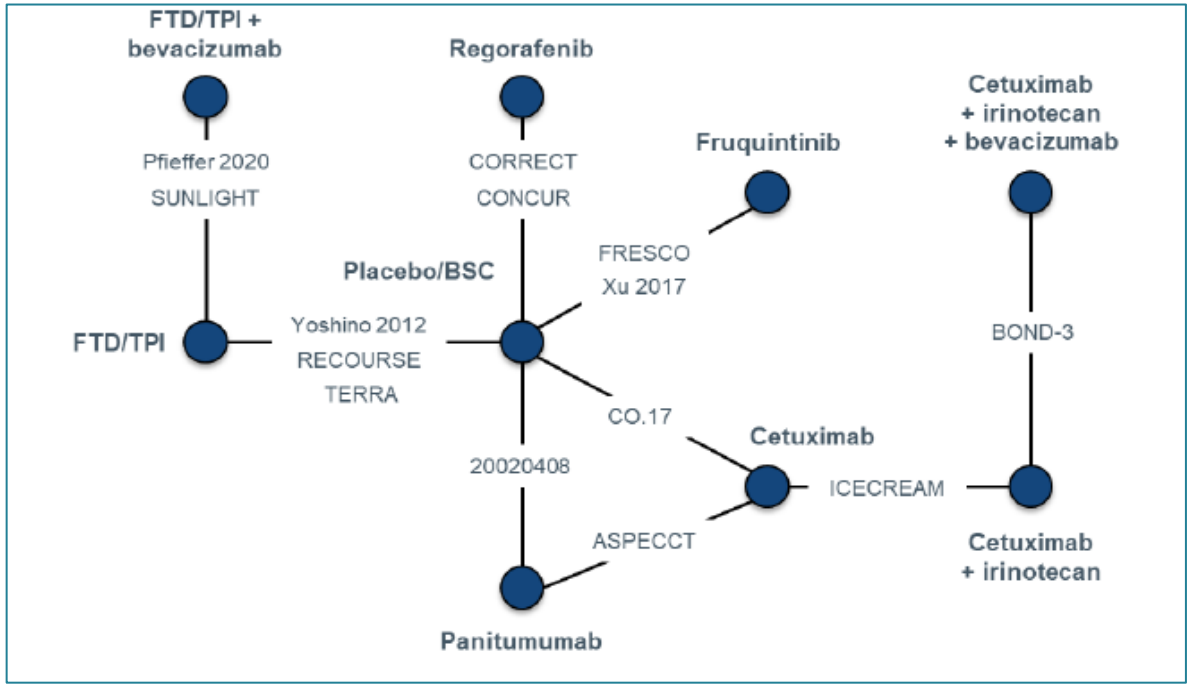
	CORRECT
Design	Double-blind, randomised, controlled two-arm phase 3 trial
Population	Adults ≥18 years with mCRC (stage 4) who had progressed disease within 3 months on approved standard treatment
Intervention	Regorafenib plus BSC
Comparator	Placebo plus BSC
Duration	Intervention arm duration of treatment: 2.8 months Comparator arm duration of treatment: 1.8 months
Primary outcome	OS
Key secondary outcomes	PFS, ORR, DCR
Locations	13 locations - Japan, USA, Germany, Italy, France, Spain, Belgium , Australia, Israel, Canada, Czech Republic, Netherlands, China, Hungary, and Switzerland (no UK patients)
Used in model?	Yes

Abbreviations: mCRC, metastatic colorectal cancer; ; OS, overall survival; PFS, progression free survival; ORR, overall response rate; DCR, disease control rate

NMA details

Company's methods for NMA are appropriate

NMA details	
Methods	Bayesian approach; random and fixed-effects models
Number of RCTs	OS – 14 RCTs, 9 treatments in network PFS – 15 RCTs, 10 treatments in network **(outcomes from 7 RCTs in NMA)**
Population	• All participants ≥18 years with mCRC • ECOG PS 0-1 (6 RCTs), ECOG PS 0-2 (1 RCT) • ≥2 prior therapies (4 RCTs), ≥1 prior therapies (2 RCTs), 1-2 prior therapies (1 RCT)
Outcomes	OS and PFS (based on reported HRs, assumed proportional hazards)



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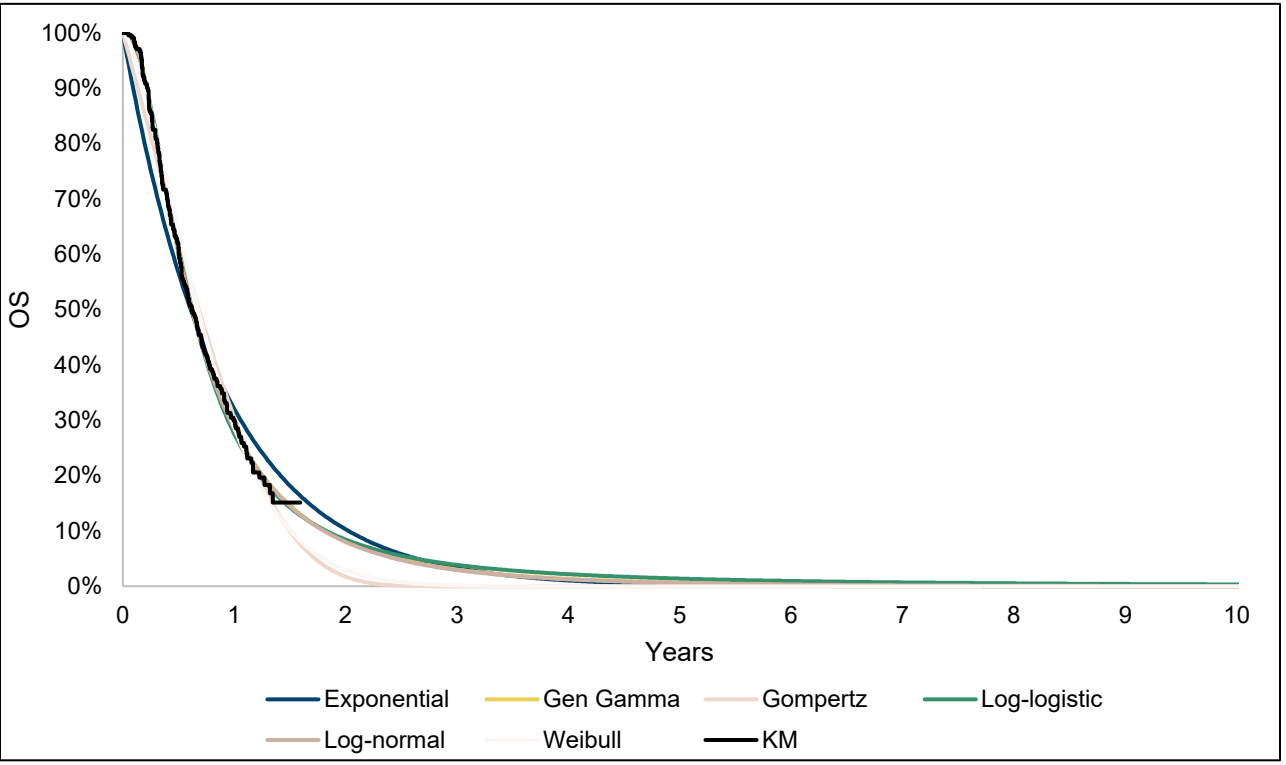
Abbreviations: ECOG PS, ECOG Performance Status; HR, hazard ratio; NMA, network meta analysis; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression free survival RCT, randomised controlled trial

*Back to main slides

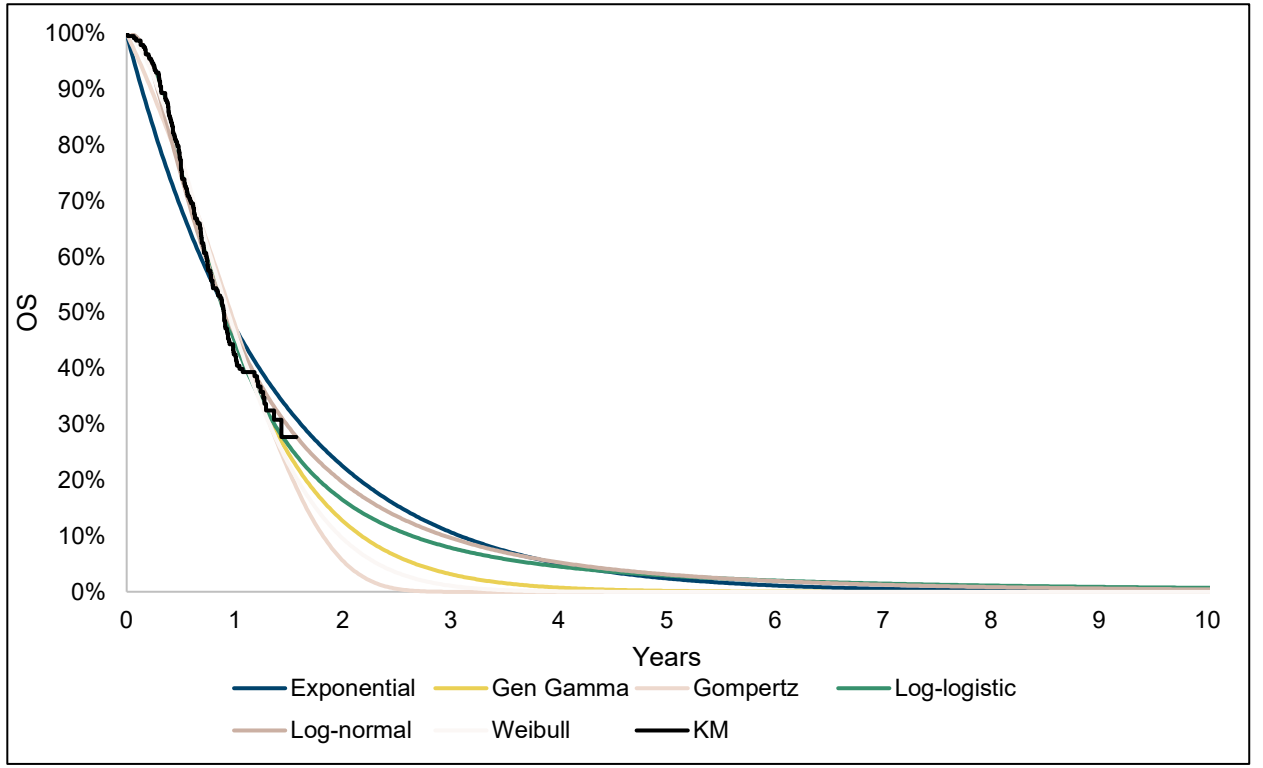
Overall survival Kaplan-Meier curves

Kaplan-Meier curves for trifluridine-tipiracil alone and with bevacizumab

Trifluridine-tipiracil monotherapy:



Trifluridine-tipiracil with bevacizumab:



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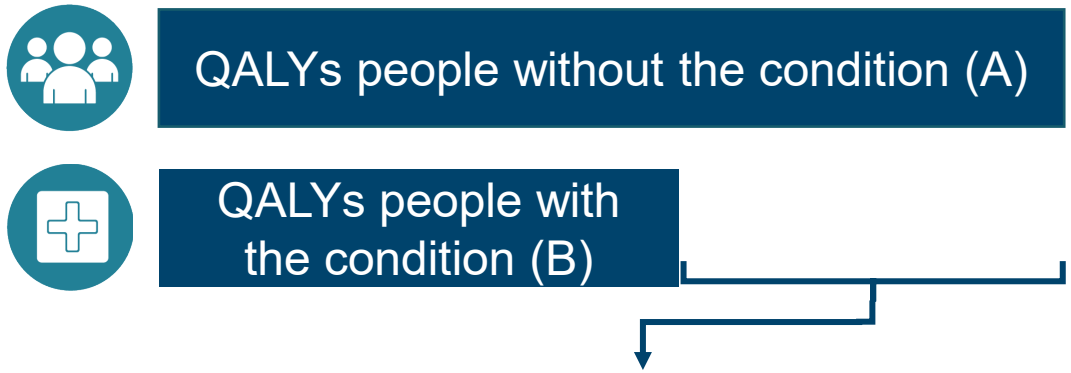
KM; Kaplan-Meier

*Back to main slides

QALY weightings for severity

Severity reflects future health lost by people living with a condition who have current standard care



Health lost by people with the condition:

- Absolute shortfall: total = A – B
- Proportional shortfall: fraction = (A – B) / A

Criteria used to decide QALY weighting

QALY weight	Absolute shortfall	Proportional shortfall
1	Less than 12	Less than 0.85
X 1.2	12 to 18	0.85 to 0.95
X 1.7	At least 18	At least 0.95

- QALY weighting can be applied based on whichever of absolute or proportional shortfall implies the greatest severity
- If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply
- Additional weight applied to QALYs within cost effectiveness calculation

Abbreviations: QALY, quality-adjusted life year

*Back to main slides

Modelling of no prior bevacizumab subgroup

EAG and company both consider subgroup analysis as **exploratory only**

	Log-normal		Weibull	
	Tri-tip+ bevacizumab	Tri-tip mono	Tri-tip + bevacizumab	Tri-tip mono
PFS - 1 year	26%	2%	23%	1%
PFS - 2 years	7%	0%	1%	0%
OS - 2 years	32%	10%	21%	4%
OS - 5 years	7%	1%	0%	0%

Table x: Model outcomes on OS and PFS after 1, 2 and 5 years

Company

- Fitted a range of parametric survival curves: most provide good statistical and visual fit
- Log-normal most appropriate to model PFS and OS, informed by clinical opinion
- For ToT, Weibull most appropriate for modelling trifluridine-tipiracil + bevacizumab and log-normal for trifluridine-tipiracil alone

EAG comments

- Chosen OS curve has substantial impact on LYGs and ICERs
- Most extrapolations are reasonable, choice should reflect plausibility of long-term projections
- Weibull more appropriate for both PFS and OS – predicts lower proportion of patients alive at 5 years (in line with EAG clinical expert opinion).
- Agrees with company for ToT modelling
- Similar subgroup data not available for regorafenib and BSC – comparisons should be interpreted **with caution**
- Company has assumed that HSUVs are the same in ITT and 'no prior bevacizumab' subgroup - there may be differences in utility across subgroups that have not been identified

What is the most plausible extrapolation curve for modelling OS and PFS in this subgroup? Company = log-normal. EAG = Weibull